ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 3 Issue 3 March 2019

Research Article

Children Hospitalized with Severe Malaria in Luanda (Republic of Angola): Time to a Administration of the First Dose of Anti Malárico After the Research Test of Plasmodium Positive No Hospital and Factors Associated with Mortality

Claudete Ginga Samutondo*, Rosa Moreira, João Pires and Júlio Leite

Field Epidemiology Laboratory and Training Program– FELTP, Medical University- UAN, Luanda, Angola

***Corresponding Author:** Claudete Ginga Samutondo, Field Epidemiology Laboratory and Training Program– FELTP, Medical University- UAN, Luanda, Angola.

Received: November 20, 2018; **Published:** February 12, 2019

Abstract

In Angola, Malaria is the leading cause of death among children under 5 years of age. From December 2015 to May 2016, all health units in Luanda reported an alarming increase in the number of cases of severe Malaria and related deaths in all age groups, especially in the 0-4 age group. We aimed to evaluate risk factors associated with high Malaria mortality rate among children <5 years of age admitted at the health units. A 1:1 age matched hospital based case control study was carried out in 142 malaria hospitalized children. A case was any child under the age of 5 years with a diagnosis of microscopically confirmed Malaria and whose outcome of hospitalization was death. A control was any child with the same diagnosis and hospitalized at the same hospital as the case, who were discharged after successful treatment. A structured questionnaire was used to collect primary data using a face to face interview with the care giver of the selected child and secondary data was obtained through desk review of the clinical files. Logistic regression models were used to identify risk factors associated with Malaria death in under five children admitted in the health units of Luanda province. All analysis were evaluated at 5% level of significance. Being ill for a period ≥7 days was significantly associated with a 135 fold times risk of death, [AOR = 135.9; (95% CI: 17.5 - 155.4), p < 0.001], waiting 12 or more hours to be administered the first prescribed drug was greatly highly associated with Malaria death, [AOR = 217.1; (95% CI: 6.6-717.8), p < 0.001]. Those who were not treated with Artemeter on admission to hospital were, [AOR = 12.4; (95% CI: 1.8 - 87.9), p < 0.001] at risk of death due to Malaria. The lethality of severe malaria cases remains high. Most of the Malaria caused deaths occur within 24 hours of admission, suggesting that pre-hospital management can have an impact on the risk of lethality. Immediate Malaria diagnosis and treatment should be put into practice in the health units. An urgent need to raise awareness of care givers to immediately seek health care is important. Malaria case management should be improved at hospital level.

Keywords: *Children; Severe; Malaria; Mortality*

Introduction

Around 3.2 billion people worldwide (almost half of the world's population) are at risk of contracting malaria. Children under 5 years of age, pregnant women and non-immune travelers from malaria-free areas are particularly vulnerable to disease when infected. Between 2000 and 2015, the incidence of malaria among risk populations decreased by 37% globally. In the same period, mortality rates among risk populations decreased 60% in the world among all age groups and in 65% among children under 5 years of age. In 2015 in the world, 214 million cases were registered with About 438,000 deaths per Malaria. 90% malaria deaths occur in sub-Saharan Africa, of which 70% in children under 5 years of age, in this African region 1 child dies from this disease every 2 minutes [1-3]. In sub-Saharan Africa, most cases of global malaria occur. In 2015, 88% of cases and 90% of malaria deaths occurred in this region [1,4]. The lethality of severe malaria cases remains high in a large part of sub-Saharan Africa. There are areas where the percentage of the population under the risk of contracting malaria is higher in relation to other places.

In Angola Malaria is endemic in the 18 provinces of the country, it is an infectious disease of perennial transmission with seasonal peaks and geographically with different levels of endemicity [5].

In Angola predominate infections caused by the *Plasmodium falciparum* (87%), followed by the vivax (about 8-10%), *Oval* (1%) and *malariae* (3%). Although several anopheline species have been identified and implicated in the transmission of the disease, the complex of the Anoptoes gambiae (SS, Melas and Arabiensis) predominates, and Anopheles funestus [5].

Malaria remains a dominant public health problem in Angola as the first cause of death due to illness, absenteeism (26 days/worker/year) and school (21 days/students/year) (From-DÚNEM, 2012). Malaria leads the list of predominant diseases in Angola with 56% of deaths [1].

In the period from three to nine September 2012, the municipality of Cuango, Province of Lunda-Norte, reported a sudden increase in the number of deaths (3 to 7 deaths) of children who presented symptomatology characterized by fever, hypocored mucous membranes and coma, Mostly from the Balabala district [6].

In 2013 in the period from January to February the province of Uíge reported the occurrence of an increase in the number of confirmed cases/day of malaria in 100 to 200 in the provincial Hospital "outbreak" with a total of 4,858 cases and 72 deaths Passion African GASPAR, 2013.

In 2014, mortality from malaria in Angola was 5,714 deaths, of which 47% occurred in pregnant women, 25% of deaths in all ages were in the province of Luanda [7].

The province reported 3,044 deaths distributed as follows: 906 in children under 5 years of age, 1185 in children aged 5 to 14 years, 17 in pregnant women and 374 deaths in adults (Office Provincial de SAÚDE de LUANDA,2015).

The factors associated with mortality from malaria are variables that directly relate to severity, consequently, to the patient's death. Patients with severe malaria in ICU hospitalization are mandatory to reduce the complications resulting from the infection. The initiation of treatment should be as early as possible, which has an impact on the patient's survival [8].

In 2014, the Ministry of Health (MINSA) of Angola proposed to reduce in 80% the impact of malaria in the country until 2015 compared with Baseline 2006 and 60% up to 2019 compared with the baseline of 2012 the morbidity and mortality of the disease. Aiming at achieving the goals recommended by the National Malaria Control Program (PNCM) with the help of national and international partners, a number of actions culminated with a remarkable decline in mortality from 20.4% in 2009 to 11.1% in 2012. The Impact of actions on malaria control was mainly due to a number of factors, from the stabilization of the populations, determined by the end of the war, the improvement of the population's nutritional situation, the Introduction and use ACTs, TDR, of the TIP, Integrated vector control, Increased coverage of the laboratory network and the Laboratory confirmation of the diagnosis Played a decisive role in this reduction. The malaria case reduction period in the province of Luanda was consistent until the beginning of 2015.

From the third quarter of 2015, the Luanda Provincial Health Office (GPSL) began to notice an increase in the notification by urban municipalities in the number of deaths due to malaria, from 388 in 2014 to 1633 in 2015. Deaths in children under 5 years old also ranged from 170 in the year 2014 to 458 in 2015. In the period from December 2015 to May 2016, all sanitary units in the urban area of the province of Luanda, both state and private, reported an alarming increase in the number of deaths and cases of severe malaria in all age groups, mainly in Age group from 0 to 4 years old. These deaths have been reported to have occurred in individuals who initially appeared at the clinical examination to be healthy but who progressed rapidly to severe malaria stage and consequently to death. In the first weeks of 2016 the situation was still worrying. The province of Luanda only in the period from January to May 2016, reported 24,832 patients hospitalized for malaria in these 3998 (16.1%) resulted in deaths, 1932 (48.3%) occurred in children younger than 5 years. Given the Situation of the province has urged the need for a thorough evaluation taking into consideration the epidemiological, parasitological and entomological parameters of the disease. This study aimed to investigate the factors associated with rapid progression of malaria mortality in hospitalized patients aged from zero to four years of age.

We intend with the results obtained, contributing to the control of factors associated with mortality from malaria in children under 5 years of age hospitalized in the sanitary units of the province of Luanda.

This work aims to evaluate the factors associated with mortality from malaria in children under 5 years in the sanitary units of the province of Luanda, 2016, in order to identify pre-hospital factors that contributed to the progression to Severe malaria among cases and controls: provenance, first signs and symptoms present and attitudes of children responsible after the onset of symptomatol-

ogy; Identify in-hospital factors that contributed to malaria death among cases and controls: hospitalization in the last 12 months, consultation with another health unit before hospitalization; Place of hospitalization, time of disease progression, presence or absence of drugs for administration of the first dose of anti-malarial, type of admission, waiting time for the administration of the first dose of anti-malarial after microscopic examination of Research of *Plasmodium*, signs and symptoms, more frequent complications, laboratory results (hemoglobin and parasitemia); Determine the independent factors associated with malaria mortality; Propose appropriate measures to control malaria mortality based on research results.

Materials and Methods

Type of study and context

An analytical study of case control 1:1 paired by age was performed in children under 5 years old with positive microscopy for malaria, hospitalized in the sanitary units of reference of municipalities in the province of Luanda.

Study period

Data collection for the study was carried out in the period of 30 April to 29 June 2016.

Place of study

The study was carried out in six reference sanitary units in Luanda.

Characterization of sanitary units

The sanitary units selected for the study are health institutions of reference and with criterion of hospitalization in the province of Luanda, namely: Hospital Geral dos cajueiros a sanitary unit designed for sanitary coverage of the Northern zone Of the province of Luanda; Hospital Municipal de Viana makes the sanitary coverage of one of the most populous municipalities in the country in the southern part of the province of Luanda, with a population estimated at more than 2 million inhabitants; General Hospital of Luanda makes sanitary coverage to neighborhoods: New life, golf 1, Golf 2, Palanca, Calemba 2, SDAs, Bondo hat and the Bita tank; The Hospital's maternal and child specialized hospitals of Kilamba kiaxi make sanitary coverage to the district's population with the same name; Hospital municipal do Sambizanga covers the population of the district of Sambizanga and the municipality of Cazenga and the municipal Hospital of Cacuaco that covers the population of the same municipality. A detailed characterization of each sanitary unit selected in this study is attached (see ANEXO2).

Study population

The study involved all hospitalized children Under 5 years of age during the period of 30 April to 29 June 2016 Selected sanitary units in the province of Luanda.

Reference population

The reference population was children under five years of age hospitalized with malaria Selected sanitary units for the study.

Sampling technique and sample calculation

The multiple-step sampling technique was used to perform this study.

First stage: Determination of municipalities

All five urban municipalities in the province of Luanda were included. The inclusion was made based on the evaluation of data in which only urban municipalities reported an increase in the number of cases and deaths: Luanda, Cazenga, Cacuaco, Viana, Belas the selected municipalities.

Second stage: Determination of sanitary units

The selection of sanitary units was made deliberately on the basis of the high number of malaria cases Reported. Thus, in each municipality, the referral hospital with the highest number of reported cases and deaths was selected. From the municipality of Luanda for having six districts were included the two sanitary units with more cases and reported deaths, thus to the municipality of Luanda Two (2), Viana one (1), Cacuaco one (1), Belas one (1) and Cazenga one (1) totaling six (6) units Sanitation in the province of Luanda.

Third stage: Selection of cases and controls

The systematic random sampling method was used for the selection of hospitalized children.

The list of all children hospitalized with malaria of all the selected sanitary units was made to obtain the total number of children during the study period. Using the sampling fraction K = n/n Where:

K: Is the size of the range;

N: Total number of hospitalized patients;

N: Calculated sample size.

After having obtained the size of the interval, the first case selected was randomly made, then it was taken out each participant using the calculated interval. The procedure for selecting participants was repeated until the calculated sample size was reached.

A control with the same age was selected for each case.

Sample calculation

The sample size was calculated using the two-aspect formula:

$$n = \left(\frac{r+1}{r}\right)\frac{(\bar{p})(1-\bar{p})(Z_{\beta}+Z_{\alpha/2})^2}{(p_1-p_2)^2}$$

Where:

n = Number of cases

(which will be equal to the number of controls);

R = 1 (couplet 1:1);

$\bar{p}$= Average proportion of people exposed, assuming that about 17% of the children < 5 years died of severe malaria during the course of their hospitalization (according to preliminary data malaria presented the overall lethality rate of 10%, being considered quite Higher in children aged < 5 years);

p1 = Proportion of people exposed (calculated, assuming OR minimum = 3);

p2 = Proportion of excess exposure 17%;

Zβ= 0.84 (assuming power 80%);

Zα = 1.96 (assuming statistical significance level = 0.05);

The minimum sample size calculated was 69 cases and 69 controls (138 in total).

Criteria for the selection of cases and controls

All patients under the age of 5 years were included, hospitalized for malaria, confirmed by laboratory, with the outcome of death or survival, in the sanitary units selected in the period from April 30th to June 29th.

Inclusion criteria for cases and controls

To be included in the study, the Children should meet the following criteria:

- Be under 5 years of age;
- have been hospitalised by malaria;
- Laboratory confirmation by Microscopy for the Plasmo dium falciparum;
- That the responsible had agreed to participate in the study and signed the informed consent.

Exclusion criteria for cases and controls

All sick children have been excluded as cases or controls:

- Hospitalized for another pathology other than malaria, the cause of hospitalization;
- Children whose clinical process was not included in the outcome signed by the physician.

Procedure for the selection of participants

Using the registration book of the emergency banks of each sanitary unit, we proceeded to list all children hospitalized for malaria in the study period. Next, the child's clinical process was surveyed to see the outcome and be grouped in the cases or in the control group. After this, the responsible was contacted by the child through the telephone number found in the clinical process to request the participation of his/her child in the study and to mark the interview.

The respondents were interviewed by the children who agreed to participate in the study, After the signature of the informed consent in order to obtain socio-demographic information related to the onset of symptoms until hospitalization.

The questionnaire was completed through the information taken from the clinical processes, such as the clinic evolution after hospitalization.

Case definition and Control

Case definition

The case was defined as any child under the age of 5 years hospitalized with the laboratory diagnosis of malaria by *Plasmodium falciparum* Confirmed microscopically and whose outcome of hospitalization was death.

Control setting

Control was defined as every child Less than 5 years hospitalized in the same hospital as the case with confirmed laboratory diagnosis of malaria by Plasmodium falciparum and who survived after hospitalization, which could be paired with the case by age.

Tool for collecting data processing and analysis

The primary data were obtained through a questionnaire and the secondaries from the patients ' clinical processes.

The data were inserted and analyzed In the statistical software Epi Info version 3.5.3 of 26-01-2011, pTo generate frequencies, proportions, averages and medians, the Bartlett test for variance in inequality between the groups of the population (Bartlett's test for inequality of population variances) uni-varied analyses were performed to study the strength of the association Between risk factors and malaria mortality in children under 5 years old expressed in terms of OR with their respective confidence intervals (CI).

All variables were considered significant when the P value was less than 0.05.

Contingency tables with Pearson chi squared test (χ^2) and paired correlations were used to identify factors associated with malaria mortality in the case group. Relevant variables with χ^2 Statistically significant were used to construct a multivariable logistic regression model with the factors associated with malaria mortality. The area under the curve Receiver operating characteristic (ROC) for discrimination and *Goodness-of-fit* was used to evaluate the adequacy of the final model. Quality control was carried out throughout the study.

Ethical considerations

The investigation protocol was submitted to the National Ethics Committee to obtain the authorization that was granted after

some corrections suggested by the same committee. The GPSL was granted authorization to carry out the study in the sanitary units that are on the jurisdiction of the same. The GPSL obtained the credential that served to acquire the authorization in the selected sanitary units. Written informed consent was obtained from each person responsible for the selected child to participate in the study. It was respected the choice of the child's guardian to participate or not or to refuse to continue if he decided to give up after giving his consent and ensured the respect and maintenance of confidentiality throughout the study.

Plan for the use and dissemination of data

The report data were disclosed to the course coordination, the directorates of the Hospital Geral dos Cajueiros, hospital municipal de Viana, Municipal Hospital of Sambizanga, specialized hospital maternal children of Kilamba Kiaxi, Municipal Hospital of Cacuaco, Provincial Health Office of Luanda, the National Directorate of Public Health of MINSA.

Results

Socio-demographic characteristics of the participants to the study

A Table The low describes the socio-demographic characteristics of the 71 cases and 71 controls included in the data analysis. The mean age for both cases and controls was 2 years [standard deviation (SD) = 1 year]. As for gender distribution only in the control group, a greater predominance of males was observed 40 (56.3%) in relation to females with 31 (43.7%).

35% of the controls and 32.4% of the cases resided in the municipality of Luanda, making this the municipality with the largest number of participants in the study. Analysis of the level of education allowed verifying that 36 (50.7%) of the cases belonged to families whose guardians had no education level while 38 (53.5%) of the controls had completed the second cycle; more cases 66 (93.0%) Whereas controls 57 (80.3%) lived in homes without channeled water.

Key factors contributing to malaria progression Severe during the pre-hospital period

The behavior and practices of guardians of children who could have significant influence on the outcome of hospitalized children since the onset of malaria symptoms until admission to the sanitary unit were analyzed as a single unit with (VP < 0.001), so having visited a healer was reported by only 14 (9.9%) cases; However 32 (45.1%) of the cases and 04 (5.6%) of the controls reported having done traditional treatment. Self-medication with conventional treatment (having taken any drug purchased in a pharmacy such as analgesic, antibiotic or anti-malarial) before seeking the sanitary unit was reported by 38.0% of the controls and 2.8% of the cases; Having gone directly to the sanitary unit shortly after the onset of symptoms was reported by 30 (42.3%) of the controls and 01 (1.4%) of the cases (Table 2).

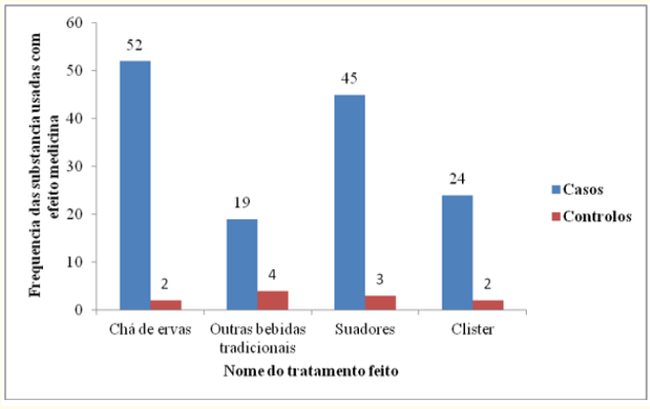
Features	Total N = 142 N (%)	Cases N = 71 N (%)	Controls N = 71 N (%)	P-Value
Average age Years DP (years)	2 (1.0)	2 (1.0)	2 (1.0)	1.000
Age groups (years):				
< 1 years	06 (4.2)	03 (4.2)	03 (4.2)	1.000
01 years old	12 (8.5)	06 (8.5)	06 (8.5)	
02 years old	62 (43.7)	31 (43.7)	31 (43.7)	
03 years old	28 (19.7)	14 (19.7)	14 (19.7)	
04th years old	34 (23.9)	17 (23.9)	17 (23.9)	
Sex				
Female	67 (47.2)	36 (50.7)	31 (43.7)	0.401
Male	75 (52.8)	35 (49.3)	40 (56.3)	
Municipality				
Beautiful	17 (12.0)	06 (8.5)	11 (15.5)	
Cacuaco	23 (16.2)	11 (15.5)	12 (16.9)	
Cazenga	28 (19.7)	19 (26.8)	09 (12.7)	
Icolo and Bengo	01 (0.7)	01 (1.4)	00	0.258
Luanda	48 (33.8)	23 (32.4)	25 (35.2)	
Viana	25 (17.6)	11 (15.5)	14 (19.7)	
Characteristics of the child responsible, type and conditions of residence				
Education level of the parent				
No instruction	44 (31.0)	36 (50.7)	08 (11.3)	<0.001
1st cycle	44 (31.0)	24 (33.8)	20 (28.2)	
2nd cycle	49 (34.5)	11 (15.5)	38 (53.5)	
Superior	05 (3.5)	00 (0.0)	05 (7.0)	
Occupation of the responsible				
Peasant	02 (1.4)	01 (1.4)	01 (1.4)	
Maid	06 (4.2)	05 (7.0)	01 (1.4)	<0.001
Private employee	33 (23.2)	09 (12.7)	24 (33.8)	
Civil servant	19 (13.4)	02 (2.8)	17 (23.9)	
Seller (a)	72 (50.7)	45 (63.4)	27 (38.0)	
Unemployed	10 (7.0)	09 (12.7)	01 (1.4)	
House structure				
Definitive Construction	126 (88.7)	61 (85.9)	65 (91.6)	0.288
Provisional construction	16 (11.3)	10 (14.1)	06 (8.4)	
Electricity				
Not	111 (78.2)	48 (67.6)	63 (88.7)	0.002
Yes	31 (21.8)	23 (32.4)	08 (11.3)	
Water				
Channeled	19 (13.4)	05 (7.0)	14 (19.7)	0.027
Tank	123 (86.6)	66 (93.0)	57 (80.3)	

Table 1: It represents the socio-demographic characteristics of cases and controls in the province of Luanda, 2016.
DP: Standard deviation

Attitude of patients after onset of symptoms	Total N = 142 N (%)	Cases N = 71 N (%)	Controls N = 71 N (%)	P-Value
He went to the healer	14 (9.9)	14 (19.7)	00 (0.0)	<0.001
He went to the Hospital	31 (21.8)	01 (1.4)	30 (42.3)	
He went to the private health office	06 (4.2)	02 (2.8)	04 (5.6)	
He went to the public health post	02 (1.4)	00 (0.0)	02 (2.8)	
Conventional treatment	29 (20.4)	02 (2.8)	27 (38.0)	
Traditional treatment	36 (25.4)	32 (45.1)	04 (5.6)	
Conventional + traditional treatment	24 (16.9)	20 (28.2)	04 (5.6)	

Table 2: It represents the distribution of the visited sites and the type of treatment to which the cases and controls were submitted after the onset of signs and symptoms, Luanda province, 2016.

No graph 1 the traditional types of treatment are specified to which the cases and controls were immediately submitted to the onset of symptoms before being hospitalized in the sanitary unit.



Graph 1: Illustrates the traditional treatment done by cases and controls, Luanda Province, 2016.

Cases and controls after the onset of symptoms before being hospitalized in the sanitary unit were subjected to one or more traditional types of treatment, namely

Herbal tea, 52 (73.2%) of the cases, two (2.8%) controls; Other beverages 19 (26.8%) of the cases, four (5.6%) of the controls; Sweers, 45 (63.4%) of the cases, three (4.2%) of the controls; 24 (33.8%) of the cases, two (2.8%) controls.

The first sign and symptom present and the type of anti-malarial administered to the cases and controls were as follows: Fever 62 (87.3%) for the cases, 55 (77.5%) for the controls; Headache 12 (16.9%) in the cases, eight (11.3%) in the controls; Diarrhea one (1.4%) in cases, one (1.4%) in the controls; Abdominal pain, three (4.2%) for the controls (VP 0.2855).

The following anti-malarial patients were administered before the hospitalization of the children

Amodiaquine orally to 15/33 cases and 03/09 of controls; Artemeter via parenteral, 04/33 for the cases, 03/09 for the controls; Artemeter-lumefantrine Oral route 13/33 to cases, 03/09 for controls; quinine oral Route 01/33 only for the cases, (VP 0.202).

Of the total of 33 children administered anti-malarial before hospitalization, 18/33 of cases and 07/09 of the controls, incorrect malarial was administered (dosage, dose, time, vomiting during oral administration) in relation to the dose Four of the cases, three of the controls; Dosage, only four for the cases; Time, five for the cases, one for the controls; Vomiting during oral administration five of the cases and three of the controls.

In-hospital factors that have contributed to malaria death among cases and controls

History during hospitalization of cases and controls

During the study period, only two of the six sanitary units (Luanda General Hospital and the Sambizanga Municipal Hospital) had all the medication and material needed to treat hospitalized children, such as; Antimalarial (quinine, Artemeter, artesunate, infusions) and disposable material such as syringes, needles, gills, systems for application of infusions and blood. The other units had a deficit of many of the materials and even some anti-malarial.

46 (67.7%) of the cases and 19 (27.1%) of the controls had a history of being seen in another sanitary unit before hospitalization (VP < 0.001); Regarding the antecedents of hospitalization for 30 (42.3%) of the cases had been the first hospital admission since the onset of symptoms and other 37 (52.1%) had been transferred from another unit and four (5.6%) had been readmitted due to disease recurrence, Regarding 53 controls (74.7%) had been hospitalized for the first time, 18 (25.3%) had been transferred and no rehospitalization due to recurrence of the disease (VP < 0.001). The mean time since the onset of symptoms until hospitalization was 13 days (SD = 5 days) for the cases and for the controls only four days (SD: 3 days), (VP 0.0002) (Table 3).

Features	Total N = 142 N (%)	Cases N = 71 N (%)	Controls n = 71 N (%)	P-Value
Hospitalization in the last 2 months	N = 140	N = 69		0.208
Yes	12 (8.6)	08 (11.6)	04 (5.6)	
Not	128 (91.4)	61 (88.4)	67 (94.4)	
Consultation in another US before internment	N = 138	N = 68	N = 70	<0.001
Yes	65 (47.1)	46 (67.7)	19 (27.1)	
Not	73 (52.9)	22 (32.3)	51 (72.9)	
Sanitary units				
HMI Kilamba Kiaxi	18 (12.7)	09 (12.7)	09 (12.7)	0.022
HG Cajueiro	36 (25.3)	18 (25.4)	18 (25.4)	
HG of Luanda	26 (18.3)	13 (18.3)	13 (18.3)	
HM Cacuaco	22 (15.5)	11 (15.5)	11 (15.5)	
HM Sambizanga	28 (19.7)	14 (19.7)	14 (19.7)	
The van	12 (8.5)	06 (8.5)	06 (8.5)	
Admission Type				<0.001
New	83 (58.5)	30 (42.3)	53 (74.7)	
Recurrence	04 (2.8)	04 (5.6)	00 (0.0)	
Transfer	55 (38.7)	37 (52.1)	18 (25.3)	
Disease progression Time				
≤ 1 day	12 (8.5)	00 (0.0)	12 (16.9)	<0.001
≥ 1 and < 3 days	10 (7.0)	00 (0.0)	10 (14.1)	
≥ 3 and < 7 days	50 (35.2)	08 (11.3)	42 (59.2)	
≥ 7 days	70 (49.3)	63 (88.7)	07 (9.9)	
Waiting time for administration of the 1st dose of antimalarial drugs after PP +				
Less than 1 hour	44 (31.0)	08 (11.3)	36 (50.7)	
of 1-3 hours	21 (14.8)	05 (7.0)	16 (22.5)	<0.001
3-11 hours	54 (38.0)	37 (52.1)	17 (23.9)	
12 hours and more	23 (16.2)	21 (29.6)	02 (2.8)	
Delay Treatment for reasons	N = 86	N = 51	N = 35	<0.001
Awaiting other Laboratory results	16 (18.6)	08 (15.7)	08 (22.9)	
Delay by Nurse (O)	47 (54.7)	32 (62.8)	15 (42.9)	
Lack of money for the purchase of drug and material	08 (9.3)	07 (13.7)	01 (2.9)	
Lack of product in community pharmacy	04 (4.7)	04 (7.8)	00 (0.0)	
Did 1st Hemo transfusion	11 (12.8)	00 (0.0)	11 (31.4)	

Table 3: It represents the in-hospital factors that influenced the outcome of the cases and controls, Luanda Province, 2016. HM: Municipal Hospital; HG: General Hospital; HMI: Maternal infant Hospital; PP +: Positive Plasmodium research.

The median time delay between hospitalization and administration of the first dose of the anti-malarial treatment for the cases was 4 hours ranging from 4 to 48 hours the maximum waiting time, for the controls the median time delay was 0 hours varying Between 0 and 24 hours (VP 0.0000).

The most frequent reasons presented for the delay at the beginning of the treatment were the delay of nursing services due to lack of staff and the expectation of the results of other laboratory tests (Table 3).

The time of permanence of cases and controls in the sanitary unit where they were hospitalized was up to 24 hours for, 42 (59.1%) of the cases and for eight (11.3%) of the controls; Up to 48 hours, 10 (14.1%) for the cases and 12 (16.9% for the controls; More than 48 hours 19 (26.8%) of the cases and 51 (71.8%) of the controls (VP 0.0000). The mean of hospitalized days for the controls was 3.5 (SD = 1.5), in relation to the cases the median was one day ranging from less than one day to eight days.

Signs symptoms, complications present between cases and controls at the time of hospitalization in the sanitary unit

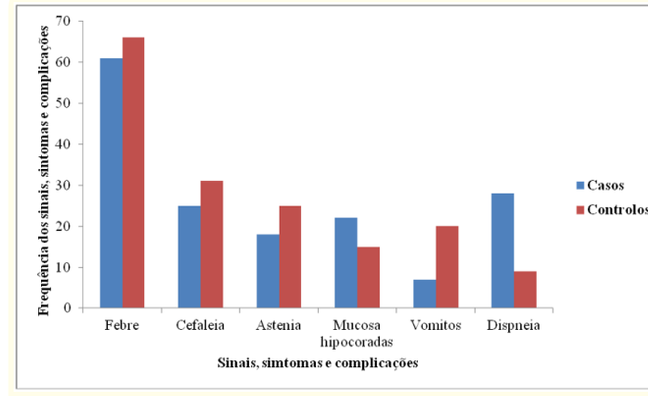
Na table 4 and the graph 2, the most frequent signs and symptoms during admission between cases and controls are presented. There was no statistically significant difference between those who presented a picture of fever, headache, hypostained mucous membranes and asthenia, but, among the cases and controls that presented a picture with multiple seizures and vomiting the difference was Statistically significant. However, more cases 17 (23.9%) than controls 7 (9.9%) reached the hospital in a coma, although this difference was not statistically significant (VP: 0.025).

Signs and symptoms	Total (N =) N (%)	Cases (N =) N (%)	Control (N =) N (%)	p-value
Fever	127 (89.4)	61 (85.9)	66 (93.0)	0.172
Headache	56 (39.4)	25 (35.2)	31 (43.7)	0.303
Asthenia	43 (30.3)	18 (25.4)	25 (35.2)	0.201
Vomiting	27 (19.0)	07 (9.9)	20 (28.2)	<0.001
Chill	11 (7.8)	3 (4.2)	8 (11.3)	0.117
Hypo-Stained Mucosae	37 (26.1)	22 (31.0)	15 (21.1)	0.181
Myalgia	02 (1.4)	01 (1.4)	01 (1.4)	1.000
Arthralgia	01 (0.7)	01 (1.4)	00 (0.0)	0.316
Hepatomegaly	16 (11.3)	11 (15.5)	05 (7.0)	0.111
Splenomegaly	23 (16.2)	15 (21.1)	08 (11.3)	0.111
Diarrhea	03 (2.1)	01 (1.4)	02 (2.8)	0.560
Most frequent complications				
Seizures	04 (2.8)	01 (1.4)	03 (4.2)	0.310
Multiple seizures	10 (7.0)	10 (14.1)	00 (0.0)	<0.001
Coma	24 (16.9)	17 (23.9)	07 (9.9)	0.025
Dispneia (N = 41)	37 (90.3)	28 (90.3)	09 (90.0)	0.976
Colúria	02 (1.4)	01 (1.4)	01 (1.4)	1.000

Table 4: It represents the most frequent signs, symptoms and complications at the time of hospitalization of cases and controls in the province of Luanda, 2016.

Laboratory results

All patients underwent haemoglobin and microscopic survey of Plasmodium At the time of admission. Patients who presented hemoglobin levels ≤ 11g/dl and severe anemia were considered as anemia patients with severe hemoglobin ≤ to 6g/dl. However, with regard to the hemoglobin values measured at the time of admission (Graph 3) The mean for the controls was 9.6 g/dl (SD: 2.6) and 6.8 g/dl (SD = 2.9) For the cases and this difference was statistically

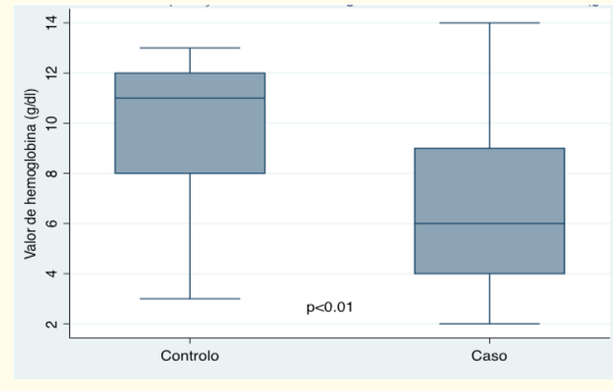


Graph 2: It illustrates the main signs, symptoms, complications presented between cases and controls during hospital admission, Luanda province, 2016.

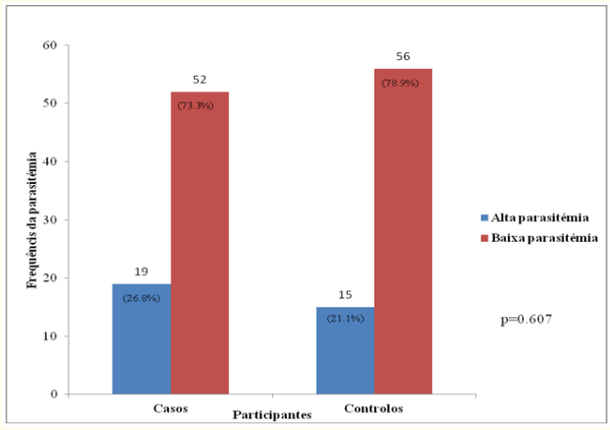
significant, p < 0.01 between the two groups. The values of parasitemia ≥ 100 000 p/mm^3 and low < 100000 p/mm^3. As shown in graph 4 The value of Parasitemia was not statistically significant between cases and controls.

Treatment	Total N = 142 N (%)	Cases N = 71 N (%)	Control N = 71 N (%)	P-Value
Quinine	54 (38.0)	40 (56.3)	14 (19.7)	<0.01
Artemeter	92 (64.8)	33 (46.5)	59 (83.1)	<0.01
Artesunato	07 (4.9)	07 (9.9)	00 (0.0)	<0.01
Penicillins	27 (19.0)	07 (9.9)	20 (28.2)	<0.001
Cephalosporin	11 (7.7)	3 (4.2)	8 (11.3)	0.117
Oxygen Therapy	37 (26.1)	22 (31.0)	15 (21.1)	0.181

Table 5: It represents the treatment administered to the case and control, in the province of Luanda, 2016.



Graph 3: Illustrates comparison of hemoglobin value between cases and controls (g/dl), Luanda Province, 2016.



Graph 4: Illustrates comparison of the value of parasitaemia between cases and controls, Luanda Province, 2016.

Treatment to which cases and controls have been submitted

A table 5 shows the type of treatment administered to cases and controls; The most used anti-malarial was artemeter, used in more controls 59 (83.1%) than in cases 33 (46.5%) Followed by quinine used in 54 (38.0%) cases and only 40 (56.3%) of the controls and lastly the artesunate which was only used in 7 (9.9%) cases. The difference in the use of the three anti-malarial between groups was statistically significant with (vp < 0.01).

Treatment	Total N = 142 N (%)	Cases N = 71 N (%)	Control N = 71 N (%)	P-Value
Quinine	54 (38.0)	40 (56.3)	14 (19.7)	<0.01
Artemeter	92 (64.8)	33 (46.5)	59 (83.1)	<0.01
Artesunato	07 (4.9)	07 (9.9)	00 (0.0)	<0.01
Penicillins	27 (19.0)	07 (9.9)	20 (28.2)	<0.001
Cephalosporin	11 (7.7)	3 (4.2)	8 (11.3)	0.117
Oxygen Therapy	37 (26.1)	22 (31.0)	15 (21.1)	0.181

Table 5: It represents the treatment administered to the case and control, in the province of Luanda, 2016.

Anti-bio therapy with either penicillin or 3rd generation Cephalosporin was used more in controls 28 (39.5%) than in cases 10 (14.1%) Although only the difference for the use of penicillin was statistically significant (VP < 0.001).

Factors associated with malaria mortality in children under 5 years of age

To identify the risk factors associated with dying from malaria, uni varied and multivariate analysis was performed. For the uni-varied analysis, all variables that had the P value less than or equal to 0.05 were selected. According to the analysis presented in Table 7 We can see that the probability of dying from malaria for the children included in this study decreases with the increase in the degree of education of its guardian; Children whose guardians had no education level were 15.5 times more at risk of dying when compared with those responsible for some level of education, [OR: 15.5 (CI: 5.6-43.0)]; Just as those who lived with Guardians who had completed the first cycle had four times the risk of dying when compared to those who lived with Guardians who had the second cycle completed [4.1 (1.7-10.1)]. The children whose guardians had no occupation or were unemployed were 76.5 times more at risk of dying when compared to those responsible for having an occupation, [or: 76.5 (CI: 6.1-96]; Regarding the type of admission (new, recurrence or transfer), the fact that the child was first seen in another institution, coming by transfer or the sanitary unit where he was hospitalized was the first option for the first contact the Results of the analysis were as follows: The probability of dying in children who had been consulted in another sanitary unit before hospitalization ranged from two to five times more in relation to those who immediately agreed to the sanitary unit where were hospitalized, [OR: 5.6 (CI: 1.5-18.0)]; In the same way that those who were transferred from another unit had three times the probability of dying from malaria than the others who directly agreed to the unit where they were hospitalized, [OR: 3.2 (CI: 1.6-6.5)]; The factors related to the delay in the administration of the drug counted from the moment after admission to the administration of the first dose, it was noted that the children who waited more than 12 hours to be given the first dose of anti-malarial were 42 times more At risk of dying when compared to those who waited less time and this risk was decreasing for those who waited less time, [OR: 42.0 (CI: 8.7-202.4] and for waiting for three to 11 hours [OR: 8.7 (CI: 3.8-20.1)]. The time of evolution of the disease calculated from the date of the onset of symptoms until receiving the first treatment after hospitalization after 7 days or more, these children were 72 times more likely to die in relation to those who had history of a Shorter period of evolution [OR: 72.0 (CI: 24.6-210.4]; The state in which the children arrived at the sanitary unit was also analyzed and those who presented with vomiting had 3.6 times the risk of dying in relation to those who did not vomit [OR: 3.6 (CI: 1.4-9.1]; Children who had been in coma at the time of hospitalization were almost three times more at risk of dying when compared to those who were not in coma [OR: (CI: 1.1-7.5)]; Children who presented a picture of anemia on admission were seven times more at risk of dying in relation to those who did not have anemia [OR: 7.0 (CI: 3.1-15.8]; The risk of dying in children who did not receive artemeter as a treatment of election to admission was five times higher than those who needed it as well as those who had received quinine therapy since admission were 4.6 times more at risk of Die when compared to those that were given another anti-malarial [or: 5.7 (CI: 2.6-12.3)] and [or: 4.6 (CI: 2.1-9.8].

Variable	OR	95% IC	P - Value
Education level of the parent			
2nd cycle	-		
1st cycle	4.1	1.7 - 10.1	<0.01
No instruction	15.5	5.6 - 43.0	
Occupation of the responsible			
Public function	-		
Peasant	8.5	0.4 - 195	0.18
Domestic	42.5	3.1 - 571	<0.01
Private function	3.2	0.6 - 16.7	0.17
Unemployed	76.5	6.1 - 963	<0.01
Selling	14.2	3.0 - 66.1	0.01
Electricity			
Yes	-	-	-
Not	3.8	1.6 - 9.2	<0.01
Water			
Channeled	-		
Tank	3.2	1.1 - 9.6	0.03
Consultation in another US prior to hospitalization			
Not	-		
Yes	5.6	2.70 - 11.67	<0.01
Sanitary Unit			
HMI Kilamba Kiaxi	-		
HG Cajueiro	5.2	1.5 - 18.0	<0.01
HG of Luanda	1.2	0.3 - 4.4	0.83
HM Cacuaco	2.2	0.6 - 8.2	0.25
HM Sambizanga	4.0	1.1 - 14.5	0.03
The van	3.6	0.8 - 17.0	0.10
Admission Type			
New/Recurrence	-		
Transfer	3.2	1.6 - 6.5	<0.01
Disease progression Time			
< 7 days	-		
≥ 7 days	72.0	24.6 - 210.4	<0.01
TEA of the 1st dose of antimalarial drugs after PP +			
Less than 3 hours	-		
3 - 11 hours	8.7	3.8 - 20.1	<0.01
12 - hour ≥	42.0	8.7 - 202.4	<0.01
Vomiting			
Not	-		
Yes	3.6	1.4 - 9.1	<0.01
Coma			
Not	-		
Yes	2.9	1.1 - 7.5	<0.01
Anemia			
Not	-		
Yes	7.0	3.1 - 15.8	<0.01
Quinine			
Not	-		
Yes	4.6	2.1 - 9.8	<0.01
Artemeter			
Yes	-		
Not	5.7	2.6 - 12.3	<0.01

Table 6: It represents the factors associated with mortality from malaria in the province of Luanda, 2016.

TEA M: Standby time for Administration of medicinal products; US: Sanitary Unit; PP +: Positive Plasmodium research.

Multivariate analysis was performed Using the binary logistic regression model with the aim of controlling confounding factors and other possible factors that could affect (underestimate or overestimate) the results. Taking into account the principle that values of p Less than 0.25 after being adjusted for other factors, can become significant, thus were placed in the model, all factors whose value of p was lower than 0.25 in the uni-varied analysis.

The independent factors associated with dying from malaria were: having remained a time equal to or greater than 12 hours without the administration of the 1st dose of anti-malarial [or: 217.1 (CI: 6.6-71.8)]; Children who waited from 3 to 11 hours for administration of the 1st dose of anti-malarial after confirming the positive GE were [OR: 10.0 (CI: 1.8-54.8)]; Have an evolution of the disease for 7 days or more [or: 135.9 (CI: 17.5-1055.4)]; Living at home without electricity [OR: 26.2 (2.3-302.6]; Not having been treated with artemeter on admission [OR: 12.4 (CI: 1.8-87.9)] and having been consulted in another sanitary unit before admission to the hospital [6.7 (CI: 1.3-34.6)].

Discussion

The strategies for reducing the number of cases and deaths due to malaria and other febrile diseases were defined as: poverty reduction, increase in the level of schooling of parents, improvement of basic sanitation, distribution of drinking water, which are reflected in Child's health.

The results in our study showed That the majority of cases were children whose guardians had low level of education, without professional occupation and who lived in difficult conditions, these factors may have influenced the negative outcome of the cases. The risk of dying for malaria was inversely proportional to the level of schooling Of those responsible for children, the lower the level of schooling the higher the risk of children dying from malaria the same was noticed in relation to the profession, the more specialized the lower the risk of the child dying for malaria, more than half of the deaths Living in households without electric light and Without running water that goes against what has been described in the WHO global technical strategy, 2015 that the disease disproportionately affects poor disadvantaged people with limited access to health units and who cannot afford the recommended treatment France SANTOS FIGUEROA, 2008; PINTO ALVES Malachi FILHO, 2005 [9].

Who in its approach to the treatment of malaria "who Guideline for the treatment of malaria, 2015" has as a key procedure that patients diagnosed with malaria should initiate treatment as soon as possible with safe and effective anti-malarial Preference during the first 24 hours after the onset of signs and symptoms [8,10].

Inappropriate treatment can lead to rapid progression of the disease leading to complicated malaria and consequently to a high lethality rate. In this study, the delay at the beginning of treatment was due to a combination of factors such as socio-economic conditions and the behavior of children responsible for the access and quality of care delivery in different health units. The first delay, to be noted in our study was marked by the socio-cultural beliefs reflected in the delay in the decision to seek health care, more cases than controls reported having gone first to seek traditional treatment or have initiated First with home treatment and only then decided to seek a sanitary unit. Almost similar results were found in the Study conducted in Malian (WILLCOX., *et al*. 2014).

The second delay usually marked by late arrival to health services, although in this study it was not directly analyzed the distance or the time that led the participants after the decision to seek health care until they reached the unit Health, but the delay to the referral hospital may be reflected in the fact that most cases have gone first to another health facility that might not be prepared to diagnose and give the appropriate treatment to which the Clinical condition of the patients required this was evident in ¾ of the cases and in only ¼ of the controls this difference was statistically significant to die by malaria; Those who have been transferred from another sanitary unit may have already been very debilitated, a condition that may have been aggravated by the general practice of only transferring the patient to another sanitary unit when he is without fully responding to the therapy Instituted Thus contributing to the increase in the time of disease progression, this second delay in our study in which children reached an average of seven days after the onset of signs and symptoms to the sanitary unit where they were hospitalized can be given because the first Units sought by the guardians of the participating children to find themselves closer to their residences, although they cannot cope with the treatment needs required by the patient. The third delay characterized by the delay in receiving high quality and appropriate care in the sanitary unit, in our study, in the group of cases seven in ten children received the first dose of anti-malarial only 12 hours Or more after being hospitalized while the children in the group of controls seven in ten received in the first 2 hours after hospitalization a significant difference and statistical significance between the cases and controls. A similar finding was reported in a study on severe malaria by *Plasmodium falciparum* in Brazil [8].

Regarding the sociodemographic characteristics of the participants, in children aged zero to five years, the group most affected by malaria was two years, in this group there was a higher frequency of signs and symptoms of disease severity and Consequently of deaths. This fact may have been because children at this stage try to socialize with the world and distance themselves from those re-

sponsible. Almost similar results were found in a hospital-based study conducted In the "rural Mozambique" African region (Balsa., *et al*. 2008).

The most common signs of severity presented by the children were respiratory distress, seizures, vomiting, having arrived in a coma and anemia. The data from our study show that the level of parasitemia is not directly related to a higher risk of death and that it was not a significant risk factor in the uni-varied or multivariate analysis, it may be that the majority of cases have Transferred by other sanitary units where they initiated anti-malarial therapy. RSimilar results were found in several studies conducted In the African region (rural Mozambique), Southwestern Tanzania, Australia, India, Malian [11-13].

In our study it was demonstrated that more than half of the deaths occurred in the first 24 hours after admission, and that some more than 25% occurred after 48 hours. Similar results were found in a study conducted in Malian in 2014 (WILLCOX., *et al.* 2014).

The choice of appropriate anti-malarial and administered at correct doses is critical for effective malaria control and reduced mortality. In this study, children who already presented signs of complications in hospitalization such as vomiting anemia and coma were statistically significant in dying for malaria. Children treated with Artemeter and quinine (drugs of choice for severe malaria) presented a higher risk of dying, this may be due to these patients were already in a very serious state at the time of hospitalization and these are the Drugs of choice for the treatment of patients with complicated malaria according to the MINSA treatment protocol [8,14]. The same protocol guides that the handling of cases of severe malaria should be done in the ICU, in our study none of the cases even those who were admitted with the signs of severity were not treated in ICU presenting thus greater risk of dying.

An interesting finding in this study was the significant difference concerning the type of anti-malarial of choice for the treatment between the cases and the controls ($p < 0.01$) and that more than half of the controls used the Artemeter intramuscularly in hospital therapy [15-35].

Conclusions

This study showed sufficient evidence that:

The socio-economic situation is a key factor in the outcome of children hospitalized for malaria, the lower the socio-economic situation of those responsible greater the risk of the child dying for malaria. Pre-hospital care such as: the state of gravity in which children arrived in the sanitary unit of hospitalization, Time of disease progression, attitudes of children responsible after the onset of symptoms, search for a private sanitary unit near the place of residence were independent risk factors associated with dying from malaria.

The in-hospital care specifically linked to the management of cases of severe malaria in the sanitary units mainly the time for the administration of the first dose of anti-malarial after the result of positive thick gout were factors associated Malaria mortality.

The majority of deaths occurred before the 24 hours of admission, showing on one side the delay of those responsible for the children arriving in the sanitary unit of hospitalization and the other due to the weakness in the provision of necessary and immediate care for the children.

Variable	OR (adjusted)	95% IC	p-value
Electricity			
Yes	-		
Not	26.2	2.3-30.6	<0.01
Consultation in another US prior to hospitalization			
Not	-		
Yes	6.7	1.3-34.6	0.02
Disease progression Time			
< 7 days	-	17.5-155.4	<0.01
≥ 7 days	135.9		
TEA of the 1st dose of antimalarial drugs after PP +			
Less than 3 hours	-		
3-11 hours	10.0	1.8-54.8	<0.01
12-hour ≥	217.1	6.6-717.8	<0.01
Artemeter			
Yes	-	-	
Not	12.4	1.8-87.9	<0.01

Table 7: It represents the multivariate model related to the factors associated with malaria mortality in Luanda province.

TEA: Waiting time for Administration: US: Sanitary unit; PP +: Positive Plasmodium research.

The in-hospital care specifically linked to the management of cases of severe malaria in the sanitary units mainly the time for the administration of the first dose of anti-malarial after the result of positive thick gout were factors associated Malaria mortality.

The majority of deaths occurred before the 24 hours of admission, showing on one side the delay of those responsible for the children arriving in the sanitary unit of hospitalization and the other due to the weakness in the provision of necessary and immediate care for the children.

Recommendations

Based on the results of the investigation we propose the following appropriate measures to control malaria mortality in children under the age of 5 years, which will be carried out by investigators of this investigation in conjunction with the following Institutions.

Bibliography

1. World Health Organization. "Malaria in the world. World Health Organization". Geneva. (2016).
2. Roberts., *et al*. "Malaria Risk Factors in children under 5 years of age in Uganda". Pubmed, Uganda, 15 (2016).
3. Ahmed S., *et al*. "Severe malaria in children: a predictive factor in the outcome and response of quinine". Original Article (2011): 54.
4. Robinson T., *et al*. "Malaria mortality indicators in African adults". Elsevier. Tanzania, (2006): 719.
5. Forte F., *et al*. "Strategic plan of the National Malaria Control Program 2016-2020". National Directorate of Public Health. Angola, (2014): 21-29.
6. Dimbo R., *et al*. "Malaria outbreak investigation in Lunda Norte province". National Directorate of Public Health. Angola. (2012).
7. Daniel A., *et al*. "Health Statistics Yearbook". Ministry of Health. Angola, (2014): 90-116.
8. Gomes AP., *et al*. "Severe malaria by Plasmodium falciparum". *Brazilian Journal of Intensive Care*, Brazil, 23 (2011): 103.
9. World Health Organization. "Worldwide technical strategy for malaria, 2016-2030". Geneva: [S.N.], (2015).
10. World Health Organization. "Malaria treatment". Geneva. 2015.
11. Dondorp A., *et al*. "A Relationship between age and the manifestations and mortality associated with severe malaria". Article, major (2008).
12. Kalinga A., *et al*. "Clinical manifestations and severe malaria outcomes among children admitted to district hospitals". Pubmed. Tanzania, (2012).
13. Sarkar J., *et al*. "Risk factors for malaria deaths: Evidence for new actions". *Bio Med Central* (2009).
14. Carvalho A., *et al*. "Guidelines and norms of conduct for the diagnosis and treatment of malaria". Ministry of Health: Angola, (2015). 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29.
15. Almeida RA., *et al*. "Early treatment of malaria, (2013).
16. Amaral EF and Guimarães L. "Malaria: Historical aspects and use of artemisinin in its treatment". Federal University of São João del-Rio, (2015): 1-9.
17. Andre ATA., *et al*. "Pathological study of malaria by Plasmodium". University Center of the Metropolitan College. United Nuclei of biological sciences and health Biomedical course, (2013).
18. Baptista RS. "Severe malaria by Plasmodium falciparum". *Brazilian Journal of Intensive Care* Brazil 23 (2011): 103.
19. Bassat Q., *et al*. "Malaria in rural Mozambique. Part II children admitted to the Hospital". Malaria Journal, Mozambique 7 (2008): 37.
20. Bennett J., *et al*. "Main practices of infectious diseases". Elsevier, New York, 2 (2010).
21. Disease Control Center. "Percentage of African population at risk of Malaria" (2013).
22. Costa MRF., *et al*. "Molecular diagnosis of malaria in a tertiary care unit". *Journal of the Brazilian Society of Tropical Medicine*, Brazil 41 (2008).
23. Dias SPCBM and Melo ML. "Sintese de drugs antimalarial hybrids". University of Cuam Portugal (2015): 3-4.
24. Fereira A., *et al*. "Malaria. What factors Determine, in the pharmaceutical industry, budgetary allocations for the investigation of a vaccine". University of Lisbon, (2015): 9.
25. Forte F., *et al*. "Strategic plan of the National Malaria Control program, 2006-2010". National Directorate of Public Health. Angola, (2007): 16
26. France T., *et al*. "Historical aspects and chemotherapy". Brazil: Teaching and Research Division, 5 (2008): 1271-1278.
27. Provincial Office of Health of LUANDA, Reporting of malaria cases and deaths, Luanda Province, Angola, (2015).
28. Image G. "Plasmodium"..
29. Image G. "Life cycle of Plasmodium inside man". (2015).
30. Roll Back Malaria; Organization World Heath. "Economic Costs of Malária". O. W. Partnership:. RBM/WHO. EUA: [s.n.]. (1998).
31. World Health Organization. "Guidelines for The Treatment of Malária". 3rd. ed. [S.L.]: [S.N.], 7 (2015). 7-37.
32. Passion., *et al*. "Malaria outbreak investigation in Uige province". Medical school. Angola. (2013).

33. Pereira EA., *et al*. "Malaria control actions: Basic Health Care Handbook". First. Ed. Basil: Ministry of Health, (2006): 3-29.

34. Silva LFRE., *et al*. "In vitro susceptibility of Plasmodium field isolates". State University of Amazonas. Manaus, (2009): 7.

35. Van-Dúnem JVD. "National Sanitary Development Plan 2012-2025". Angola: Ministry of Health 2 (2012): 35.

Volume 3 Issue 3 March 2019